

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 29

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DONALD J. KYLE and
ROGER N. HINER

Appeal No. 1997-0100¹
Application 08/167,051²

HEARD: October 12, 2000

Before WILLIAM F. SMITH, SCHEINER and GRIMES , Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

¹ As a preliminary matter, we note that this appeal is related to appeals in Application Serial Nos. 08/302,988 and 08/359,642 (Appeal Nos. 1997-1309 and 1997-2518), also heard on October 12, 2000. We have considered the three appeals together.

² Application for patent filed December 16, 1993.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 5 through 17, 21, 22, 41 and 42, all the claims remaining in the application. Claims 41 and 42 are reproduced as an Appendix to this opinion. 5

The references relied on by the examiner are:

Patchett et al. (Patchett)	4,483,850	Nov. 20, 1984
Stewart et al. (Stewart I)	4,801,613	Jan. 31, 1989
Stewart et al. (Stewart II)	4,923,963	May 8, 1990
Eur. Pat. App. (Henke I)	0 370 453	May 30, 1990
Eur. Pat. App. (Henke II)	0 413 277	Feb. 20, 1991

Krapcho et al. (Krapcho), "Angiotensin-Converting Enzyme Inhibitors. Mercaptan, Carboxyalkyl Dipeptide, and Phosphinic Acid Inhibitors Incorporating 4-Substituted Prolines," Journal of Medicinal Chemistry, Vol. 31, No. 6, pp. 1148-1160 (1988).

Hock et al. (Hock), "Hoe 140 A New Potent and Long Acting Bradykinin-Antagonist: In Vitro Studies," Br. J. Pharmacol., Vol. 102, pp. 769-774 (1991).

Claims 5 through 17, 21, 22, 41 and 42 stand rejected under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on Henke I, Henke II, Stewart I, Stewart II, Hock, Patchett and Krapcho. We reverse the rejection and enter a new ground of rejection under the provisions of 37 CFR § 1.196(b).

BACKGROUND

As explained in the specification, pages 1 through 3:

Bradykinin (BK) is a nonapeptide generated as a result of the activity of kallikreins, a group of proteolytic enzymes present in most tissues and body fluids, on kininogens.

Bradykinin, and its physiologically important related peptides . . . exhibit physiological actions which qualify them as mediators of inflammatory reactions, hypotensive states, and pain. Bradykinin is overproduced in pathological conditions such as septic shock, anaphylaxis, rhinitis, asthma . . .

In addition to its analgesic and proinflammatory effects, bradykinin is a vasodilator. Because of its ability to lower blood pressure, bradykinin has been implicated in the pathogenesis of several shock syndromes . . . Bradykinin is also a potent bronchoconstrictor . . .

Thus a bradykinin inhibitor or bradykinin receptor antagonist is expected to possess a number of desirable biological effects in the treatment, for example, inflammation, septic shock, asthma, burn pain, rhinitis and allergy.

According to appellants, the present invention is directed to bradykinin antagonists “that act as specific and competitive inhibitors of the biological activities of bradykinin,” wherein the L-Pro at position seven of the native bradykinin is replaced by D-Phe or D-Tic, and the L-Phe at position eight is replaced by a hydroxyproline ether or a thioether derivative (Brief, page 3).³

DISCUSSION

All of the pending claims stand rejected as obvious over Henke I, Henke II, Stewart I, Stewart II, Hock, Patchett and Krapcho.

³ Tic is the abbreviation for 1,2,3,4-tetrahydroisoquinoline-3-ylcarbonyl.

Henke I, Henke II, Stewart I, Stewart II and Hock disclose bradykinin antagonists differing from certain of the claimed peptides in the position corresponding to amino acid position eight (Phe) of native bradykinin. For example, many of Henke's peptides have hydroxyproline at position eight, while Hock's antagonist, Hoe 140, has Oic⁴ at that position; claims 5 through 17, 21, 22 and 41, on the other hand, require a hydroxyproline ether or a thioalkyl ether at position eight.

According to the examiner, Patchett teaches that "the heterocycles hydroxyproline or hydroxyproline ether or thioether derivative or Oic are functionally equivalent," while Krapcho teaches that "proline substituted derivatives incorporating as the substituents an alkyl or aryl or alkoxy or aryloxy or alkylthio or arylthio group are more potent in vitro." Examiner's Answer, page 5.

It is well established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996) (citation omitted).

The examiner believes that "it would have been obvious . . . to replace the residue hydroxyproline or Oic at position eight of the Henke or Hock . . . peptide sequence with a

⁴ Oic is the abbreviation for cis-endo-octahydroindole-2-carbonyl.

hydroxyproline ether or thio ether derivative” because “replacement of one heterocyclic compound with another would expectedly result in a peptide having a similar Bk antagonist activity;” and “said heterocyclic compounds are known to be functionally equivalent or would have a greater potency in vitro.” Examiner’s Answer, pages 5 and 6. In our judgment, the examiner’s reasons for combining these references will not withstand scrutiny.

Patchett discloses a generic structural formula for peptide inhibitors of angiotensin converting enzyme (ACE). There are 26 alternatives suggested for the “heterocyclic elements” of the inhibitors (among them hydroxyproline derivatives and Tic). The examiner has not explained how interchangeability of these substituents in ACE inhibitors is at all relevant to the modification of bradykinin antagonists. There is no evidence of record that bradykinin and ACE (or their inhibitors/antagonists) are similar in structure or function; indeed, appellants maintain that ACE inhibitors and bradykinin antagonists have “diametric effects and functions,” at least with respect to modulating blood pressure (Brief, pages 20 and 21). Nor do we see anything in Patchett to indicate that the substituents listed are recognized as universal functional equivalents. Thus, we agree with appellants that “even if the heterocyclic compounds are functionally equivalent in ACE inhibitors, they are not necessarily functionally equivalent in bradykinin antagonists” (Brief, page 20).

Krapcho also concerns ACE inhibitors and teaches that “analogues of . . . inhibitors with hydrophobic substituents on proline were more potent in vitro than the corresponding unsubstituted proline compounds” (Abstract). Given the different functions and effects of ACE inhibitors and bradykinin antagonists, we see nothing in this reference that suggests anything, negative or positive, about the consequences of including hydroxyproline ether or thioalkyl ether substituents in bradykinin antagonists.

We have no doubt that the prior art could be modified in a manner consistent with appellants’ specification and claims, but the fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested its desirability. In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Here, we find no reason or suggestion stemming from the prior art which would have led a person having ordinary skill to the claimed method. In our opinion, the only reason or suggestion to combine the references in the manner proposed by the examiner comes from appellants specification. Accordingly, we find that the examiner’s initial burden of establishing a prima facie case of obviousness has not been met.

The rejection of claims 5 through 17, 21, 22, 41 and 42 under 35 U.S.C. § 103 is reversed.⁵

⁵ Having determined that a prima facie case of obviousness has not been established, we find it unnecessary to comment on appellants’ arguments regarding the unexpected properties of the claimed antagonists (Brief, pages 24 through 26).

NEW GROUND OF REJECTION UNDER 37 CFR § 1.196(b)

While we have reversed the examiner's rejection of all the pending claims under 35 U.S.C. § 103, that is not to say that claim 42 is patentable over the references of record. Under the provisions of 37 CFR § 1.196(b), we enter the following new rejection:

Claim 42 is rejected under 35 U.S.C. § 102(b) as anticipated by Hock.

Claim 42 is considerably broader than any of the other claims on appeal in that the alternatives for the residue at position eight of the Bradykinin antagonist (position I in the claim) include Oic and Tic, in addition to hydroxyproline ethers and thioalkyl ethers. Hock discloses a bradykinin inhibitor with a formula corresponding to that of the claimed inhibitor at each position. See Hoe 140, Figure 1.

TIME PERIOD FOR RESPONSE

This opinion contains a new ground of rejection pursuant to 37 CFR § 1.196 (b) (amended effective Dec. 1, 1997, by final rule notice, 62 Fed. Reg. 53,131, 53,197 (Oct. 10, 1997) 1203 Off. Gaz. Pat. & Trademark Office 63, 122 (Oct. 21, 1997)). 37 CFR § 1.196 (b) provides that, "A new ground of rejection shall not be considered final for purposes of judicial review."

37 CFR § 1.196 (b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with

Appeal No. 1997-0100
Application 08/167,051

respect to the new ground of rejection to avoid termination of proceedings (37 CFR

§ 1.197 (c)) as to the rejected claims:

(1) Submit an appropriate amendment of the claims so rejected or a showing of facts relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the application will be remanded to the examiner. . . .

(2) Request that the application be reheard under § 1.197 (b) by the Board of Patent Appeals and Interferences upon the same record. . . .

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED; 37 CFR 1.196 (b)

WILLIAM F. SMITH
Administrative Patent Judge

TONI R. SCHEINER)
Administrative Patent Judge

ERIC GRIMES
Administrative Patent Judge

)
)
)
)
)
) BOARD OF PATENT
) APPEALS AND
)
) INTERFERENCES
)
)
)

Appeal No. 1997-0100
Application 08/167,051

Gary M. Nath
Nath and Associates
1030 Fifteenth Street, N.W.
Sixth Floor
Washington, D.C. 20005

TRS/jlb

APPENDIX

41. A peptide having the formula:

N-A-B-C-D-E-F-G-H-I-J-Cn

wherein N is hydrogen;

A is selected from the group consisting of L-Arg, D-Arg, Lys-Lys, and Lys;

B is selected from the group consisting of L-Arg, D-Arg, and Lys;

C and D are independently selected from the group consisting of Pro, dehydroPro, and 4Hyp;

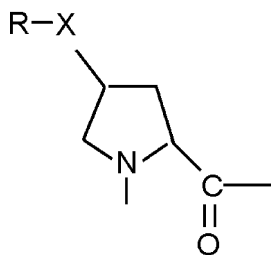
E is Gly;

F is selected from the group consisting of Phe, Leu and Thi;

G is direct bond or is selected from the group consisting of Ser and Thr;

H is selected from the group consisting of D-Phe and D-Tic;

I is a compound having the formula:



wherein R is selected from the group consisting of methyl, ethyl, propyl, isobutyl, cyclohexylmethyl, allyl, prenyl, methallyl, benzyl, phenyl, nitrophenyl, phenylpropyl, and methylbutyl, and wherein X is sulfur or oxygen;

J is Arg;

Cn is a hydroxyl group;

and pharmaceutically acceptable salts thereof.

42. A peptide having the formula:

N-A-B-C-D-E-F-G-H-I-J-Cn, wherein

N is hydrogen;

A is D-Arg;

B is Arg;

C and D are independently selected from the group consisting of Pro and 4Hyp;

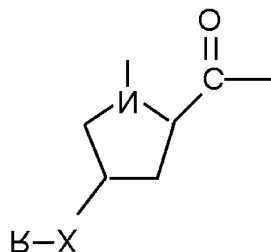
E is Gly;

F is selected from the group consisting of Phe, Leu, and Thi;

G is a direct bond or is Ser;

H is a compound of the D-configuration selected from the [sic group] consisting of D-Phe and D-Tic;

I is selected from the group consisting of Oic, Aoc, Tic and compounds of the formula:



Appeal No. 1997-0100
Application 08/167,051

wherein R is selected from the group consisting of methyl, ethyl, propyl, isobutyl, cyclohexylmethyl, allyl, methallyl, prenyl, benzyl, phenyl, nitrophenyl, phenylpropyl, and methylbutyl, and wherein X is either sulfur or oxygen;

J is Arg;

Cn is a hydroxyl group;

and pharmaceutically acceptable salts thereof.